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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,568	08/03/2001	Udo Baron	BBI-088CPADV2	9670

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/922,568	BARON ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-50* is/are pending in the application.

4a) Of the above claim(s) *33-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32 and 40-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 32-50 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 4/25/03 is acknowledged. During a telephone conversation with Applicants' representative on 7/8/03, Applicants further elected claims directed to SEQ ID NO:1.

Applicants traverse the restriction requirement on the ground(s) that any DNA binding domain can be used in the invention of Group I. Further, Applicants argue that the invention of Groups I and II should be rejoined because a search of both wild type and mutant Tet repressor can be made without serious burden. Applicants also argue that more than one sequence should be examined because MPEP states that up to ten sequences may be examined in a single application. Moreover, Applicants argue that all claimed sequences were examined in the parent applications.

This is not found persuasive because the inventions of Groups I-VI are patentably distinct for reasons set forth of the record mailed on 3/25/03. A search of one group is not co-extensive with the search of another, therefore, a search of all six groups in a single application is burdensome. As stated in the previous office action, the requirement of examining a single sequence in an application is due to the now very high and undue burden for examining more than one sequence which is caused by the continued exponential increase of size of the sequence databases to be searched for each sequence, resulting in a corresponding increase in computer search time and examiner time for reviewing the computer search results. However, for the sole

purpose of expediting the application, Groups I-VI are rejoined. The invention will be examined to the extend that the invention is directed to a transgenic animal comprising SEQ ID NO:1.

Accordingly, claims 33-39 are withdrawn from consideration for being directed to non-elected subject matter. Claims 32, 40-50 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, 40-50 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

<u>The nature of the invention:</u>

Claims 32 and 40-50 are drawn to transgenic non-human animals comprise a transgene (integrated in the genome of the transgenic animals) encodes a fusion protein comprising a first polypeptide comprising a DNA binding domain operatively linked to a second polypeptide comprising a transcriptional activation domain comprises at least one copy of a mutated acidic region of herpes simplex virus VP16 consisting SEQ ID NO: 1. The claims are further drawn to such a transgenic non-human animal wherein the first polypeptide is a Tet repressor which binds to a tet operator sequence in the presence of tetracycline or a tetracycline analog, or GAL4, LexA, LacR or steroid hormone receptor.

The state of the art and the level of predictability in the art:

As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Comparing to generation of transgenic mouse, transgenesis in the larger mammals encounters a number of limitations including longer gestation times, reduced liter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes (see Mullins J.Clin. Invest. 1996, Vol.98, no.11, S37-40, page S37, 2nd paragraph). Seidel (J. Anim. Sci. 71(Suppl. 3):26-33, 1993, see abstract) also noted "In the case of livestock species...Characterizing a transgenic line often is a greater logistical undertaking than making the transgenic founder. Ideally, animals should be evaluated for the transgenic trait as well as for absence of undesirable side effects in both sexes in both the hemizygous and homozygous transgenic states. Producing homozygous transgenic animals requires mating relatives, resulting in inbreeding. Characterization of transgenic lines takes many years in species with long generation intervals." Investigators observed lower yields of a

recombinant protein in transgenic mice when they used a construct designed for expression in ovine (see Mullin et al., page S38, 2nd col., 1st paragraph, lines 40-46). The variation in expression levels between different cell lines and species may be attributed to host genetic background, the site of chromosomal insertion and absence of specific transcription factors.

Hammer et al (Cell 63:1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rats demonstrated most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in widely different phenotypic responses. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors.

Introduction of foreign DNA into fertilized oocytes, for example by microinjection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene (see Mullins, S37, 2nd col., 2nd paragraph). Therefore, the production of transgene in all the non-human species will be highly variable and unpredictable. Even if the transgenic animals are produced, it is highly unpredictable whether such transgenic animals will express the transgene to a level high enough to enable the development of same phenotype in all the transgenic animals.

In view of the technical limitations in the art of making transgenic animal, one skilled in the art would have to rely on the teaching of the specification to make the non-human transgenic animal as claimed.

The breadth of the claims and the teaching of the specification:

The breadth of claim encompasses all animals (e.g. mouse, fish, birds, insects etc.) comprising a transgene encodes a fusion protein comprising a first polypeptide comprising a DNA binding domain operatively linked to a second polypeptide comprising a transcriptional activation domain comprises at least one copy of a mutated acidic region of herpes simplex virus VP16 consisting SEQ ID NO: 1. The specification only discloses general methods of producing transgenic animal. However, the specification does not provide any guidance as to how an artisan would have addressed the art recognized limitations of producing transgenic animals. For example, the specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been functional in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype. If not, what steps would have been taken to address these issues? Therefore, the breadth and scope of the claims surpasses that is enabled by the instant specification.

In view of the teachings of art, as cited above, the teaching of the specification and the working examples provided by the specification is not sufficient to overcome the art recognized unpredictable nature of transgenic animal phenotype. Therefore, one skilled in the art would have to engage in an undue amount of experimentation to use the claimed invention at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 40-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "a fusion protein which activates transcription" renders the claims indefinite because it is unclear the transcription of which gene is activated by the fusion protein. As such, the metes and bounds of the claim cannot be established.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

Celine Qian, Ph.D.
July 11, 2003